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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/058,630	01/28/2002	Michael L. Camilleri	07039-355001	3436

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	13

DATE MAILED: 01/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,630	CAMILLERI ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 5, 2003 has been entered.

2. Claims 1-5 and 8-14 were pending. Applicants' amendment filed June 10, 2003 has been entered. Applicants amended claims 1 and 12. Applicants' amendments overcame the following rejections: rejection of claims 1, 8 and 9 under 35 U.S.C. 112, second paragraph and rejection of claims 1-5 and 8-14 under 35 U.S.C. 102(a) over Kong et al.

3. Claims 1-5 and 8-14 are pending and will be examined.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-5 and 8-14 are broadly drawn to methods of for predicting patient's responsiveness to a 5-HT3 receptor antagonist based on determination of the genotype of the promoter region of patient's serotonin transporter (5-HTTP) gene, by correlating the presence of the long/long (= ins/ins) variant with greater responsiveness to the 5-HT3 receptor antagonist. However, as will be further discussed, there is no support in the specification and prior art for the method. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The amount of direction and guidance presented

Applicants describe serotonin (5-hydroxytryptamine or 5-HT) as a neurotransmitter that modulates sensorimotor functions in the digestive tract (page 1, lines 12-18). Applicants state that clinical trials established a beneficial effect of alosetron, a 5-HT3 receptor antagonist, in the relief of irritable bowel syndrome (IBS) symptoms (page 1, lines 26-28; page 4, lines 15-22). Applicants assert that effectiveness of the 5-HT3 antagonist treatment may be related to the genotype in the promoter region of the 5-HTTP gene (page 2, lines 6-16). Applicants provide guidance of how to determine presence of the 5-HTTP gene promoter region polymorphism (page 5, lines 27-32; page 6), how to correlate the genotype with patient's responsiveness to the 5-HT3 antagonist, using such

measures as colonic transit time, for example (page 7, 8; page 9, lines 1-15), and how to effect treatment of patients with diarrhea-predominant IBS (page 9, lines 18-32; page 10, lines 1-26).

The presence or absence of working examples

Applicants conducted a study of 23 patients with diarrhea-predominant IBS, who were enrolled in therapeutic trial with alosetron (Example 1). Patients' genotypes of the 5-HTTP gene promoter region were determined (Example 3). As a measure of alosetron effectiveness, measurement of colonic transit was performed (Example 2). In Example 6, Applicants present a conclusion that long/long variant of the 5-HTTP gene promoter region was associated with a higher response to alosetron, as measured by colonic transit.

Applicants have not presented any evidence that any other 5-HT3 receptor antagonist has similar association with a long/long variant of the 5-HTTP gene promoter region or alleviation of IBS symptoms as measured by colonic transit. Applicants have not presented any evidence that an association can be found between a long/long variant of the 5-HTTP gene promoter region and patient's responsiveness to any 5-HT3 receptor antagonist in any condition which is treated with such antagonists.

The unpredictability of the art and the state of the prior art

Applicants results contradict result of a study by Kong et al. (WO 2001/61039; cited in the previous office action), in which 219 female human subjects enrolled in clinical trial for treatment of IBS with alosetron were genotyped to determine the variant of the promoter in the 5-HTTP gene (Example 1). The genotypes were correlated with subjects' response to alosetron (Example 2), as assessed by relief of IBS symptoms, and it was found that subjects with the del/del (= short/short) genotype showed increased therapeutic response to alosetron (Fig. 3), which is directly opposite to

Applicants' findings. One reason for this may be a smaller size population sample of Applicants' study, but, as indicated by the publications cited below, the problem of serotonin-based regulation of digestive tract responses is a very complex one.

For example, as pointed out by Scherl et al. (The Pharmacogenomics J., vol. 3, p. 64-66, 2003), serotonin is a neurotransmitter which binds to more than 20 receptor subtypes, including the non-selective 5-HT3 receptor (which is a cation channel) and a G-protein 5-HT receptor. Serotonin therefore controls different aspects of the gut's sensorimotor function. The 5-HT3 receptors influence colonic transit, however, actions of alosetron show gender-related effectiveness, however even with this respect the findings are not uniform (page 65, second paragraph). Finally, Scherl et al. summarize the results of the study of Camilleri et al. (one of the Applicants), pointing out that

"The investigations were unable to correlate variability in SERT-P polymorphisms with gender-specific enhanced alosetron efficacy. Another limitation of the current study was that few of the patients had the short polymorphism, so that this group was under-represented. Future studies evaluating the role of short polymorphisms of SERT-P in gender-specific clinical responses of D-IBS to 5HT3 antagonists are required. Pharmacogenomic correlation of serotonin- transporter polymorphisms and alesotron response is a powerful research tool that may aid in stratifying individual variation in clininical response of IBS patients." (page 65, last paragraph) (emphasis added).

Gershon (Rev. Gastroenterol. Dis., vol. 3, suppl. 2, pp. S25S34, 2003) discusses roles played by serotonin in the functioning of enteric nervous system (ENS).

Gershon points to the feedback relationship between the ENS and CNS (central nervous system) as potentially significant in the pathogenesis of IBS, which is a collection of symptoms, and may, because of limited ways that gut can manifest abnormal behaviour, reflect a variety of

disorders (page S27, last paragraph; page 28, first paragraph). Further, the interactions of serotonin (5-HT) within the gut are very complex. 5-HT is secreted by enteroendocrine cells (ECs) in response to intraluminal pressure or chemical stimuli, and plays a role in the initiation of peristaltic and secretory reflexes (page S28, third paragraph; Fig. 2). 5-HT the interacts with a number of receptors:

"Enteric neurons have been found to express 5-HT1A, 5-HT1P, 5-HT2A, 5-HT2B, 5-HT3, and 5-HT4 receptors; however, of these, only 5-HT1P, 5-HT3, and 5-HT4 exert excitatory actions on enteric neurons. Neither 5-HT3 nor 5-HT4 antagonists are able, by themselves, to abolish peristaltic and secretory reflexes, although both types of antagonist can alter intestinal motility. These observations suggest that neither peristaltic nor secretory reflexes are initiated by 5-HT3 or 5-HT4 receptors. Instead, these 5-HT receptor subtypes probably modulate mucosa-initiated reflexes by affecting neurotransmission within the ENS and, indeed, it is possible to abolish peristaltic reflexes by inhibiting both 5-HT3 and 5-HT4 receptors simultaneously." (page S28, third paragraph).

Further, Gershon points to the fact that even though alosetron does seem to have an effect in the treatment of IBS symptoms in female patients, it may exert the constipating effect by interfering with small proportion of ENS synapses at which transmission is mediated by 5-HT (page S30, first paragraph). Sine the 5-HT3 receptors are responsible for transmission of signals from the bowel to the brain, antagonists of 5-HT3 receptor, such as alosetron, are used to alleviate nausea associated with cancer chemotherapy and and symptoms of visceral hypersensitivity of diarrhea-predominant sensitivity in IBS (page S30, third paragraph).

The role of 5-HT transporter (or SERT) is to remove serotonin from circulation. If SERT is inhibited, 5-HT receptors become desensitized and peristaltic reflexes are lost, as observed in mice

which lack SERT. The action of 5-HT leads in such mice to diarrhea, but as the receptors become desensitized in the constant presence of 5-HT, the colorectal motility slows and mice become constipated. This cycle mimics symptoms of IBS patients (page S31, second paragraph). The reason that the mice lacking SERT or humans having SERT not operating properly survive, is the fact that other transporters, such as dopamine transporter (DAT) and organic cation transporters (OCTs) are able to reuptake 5-HT, but to a much lesser extent (page S31, third paragraph).

Finally, Gershon describes the self-correcting mechanism of 5-HT inactivation: "The relationship among neurotransmitters, receptors, and transporters, which are collectively responsible for neurotransmission, is so closely interknit that a perturbation in one affects others. As a result, the sensitivity of 5-HT3 receptors and their propensity to become desensitized both change in SERT knockout mice. The concentration-effect curve for activation of 5-HT3 receptors shifts to the right, indicating that the 5-HT sensitivity of these receptors decreases. The receptors also become desensitized more readily. These changes are secondary to a downregulation in the expression of the B subunit of the 5-HT3 receptor. (The receptor is a dimer of A and B subunits.) Both the decrease in sensitivity and the increased tendency of the receptors to become desensitized can be characterized as adaptations to an internal milieu of increased 5-HT availability. Both changes tend to prevent the effects of receptor stimulation from becoming excessive.". Therefore, as can be seen from the above facts, interplay between the serotonin receptors and transporters is a very complex one, and the role played by either the serotonin transporter or 5-HT3 receptor in IBS is not clear.

A study performed by Pata et al. (Am. J. Gastroenter., vol. 97, pp. 1780-1784, 2002) examined a relationship between the SERT gene polymorphisms and the IBS. Pata et al. examined the promoter region polymorphism in 54 patients with IBS and 91 healthy subjects (Abstract; page 1781, paragraphs 1-6). They also divided the IBS patients into three groups, diarrhea-predominant

(n = 18), constipation-predominant (n = 26) and alternating diarrhea and constipation (n = 10) (Abstract). Pata et al. Made the following conclusions from examination of the data: a) there is no statistically significant difference in the presence of the SERT gene promoter region polymorphism between IBS and control groups (Table 2); b) the S/S (= short/short) genotype frequency was higher in the constipation-predominant group as compared to the diarrhea-predominant and diarrhea-constipation groups, but not significantly different from the control group (page 1782, first paragraph); c) the S/S (= short/short) genotype frequency was lower in the diarrhea-predominant and diarrhea-constipation groups, and lower than in the control group (page 1782, first paragraph); d) no difference was found between the frequencies of L/L (= long/long) genotype within the IBS groups and between the IBS and control group (page 1782, first paragraph); and, e) the L/S (= long/short) genotype frequency was higher in the diarrhea-predominant group as compared to the constipation-predominant and diarrhea-constipation groups, and higher than in the control group, but there was no significant difference in the L/S genotype frequency between the three IBS groups (page 1782, first paragraph). Pata et al. conclude with the following statements:

"... the presence of the S/S allele may be acting as a protecting factor for diarrhea, so one may speculate that serotonin uptake was slower in constipation predominant patients than in diarrhea predominant and diarrhea constipation patients. This reflection appears to be at odds with the bowel motility-increasing effect that serotonin is known to have, but it should not be forgotten that studies investigating the relationship between IBS and serotonin have been concerned with 5-HT receptors and postreceptor events (citation omitted). There are not enough studies attempting to determine the relationship between the SERT's gene functional capacity and receptor interaction and bowel functioning.." (emphasis added; page 1782, last paragraph; page 1783, first paragraph).

"In conclusion, it was found that SERT is not a key factor in determining whether or not an individual will get IBS" (page 1783, last paragraph).

Therefore, the overall picture that emerges from the above publications is of uncertain correlation between the genotype of the SERT gene promoter region and IBS, lack of clarity of the roles played by SERT and 5-HT3 receptors in IBS, as well as very complex 5-HT transporter-receptor interactions and feedback interactions between ENS and CNS, which make it difficult to determine with certainty that any single gene or receptor is responsible for IBS symptoms.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to determine whether treatment with 5-HT3 receptor antagonists in any disease (including IBS) for which such antagonists are used correlates with the promoter region polymorphism of the SERT gene. First, large-scale population study would have to be performed to correlate a presence of the promoter region polymorphism of the SERT gene with any disease in which 5-HT3 receptor antagonists are used. Then it would need to be determined whether any of these compounds affect any other 5-HT receptors or transporters. Finally, functional interactions between SERT and 5-HT3 receptors in any type of disease suspected on SERT involvement would need to be determined. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the antagonist-receptor effects in vivo depend upon numerous known and unknown parameters such as the

complex interactions of 5-HT receptors and transporters, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the 5-HT3 receptor antagonists for in vivo treatment as broadly claimed (i.e encompassing a treatment in any condition associated with 5-HT3 receptor). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the contradictory teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

6. No claims are allowed. No references were found teaching or suggesting claims 15 and 8-14, but they are rejected for reasons given above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

The examiner will move to the new office in Alexandria on January 8, 2004. The new phone number in that office is (571) 272-0789. Gary Benzion will move to the new office on January 22, 2004. His new phone number is (571) 272-0782.

TS
December 26, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER